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FIVE SCIENCE PARK • NEW HAVEN, CT 06511 • TEL. 203.773.1450 • FAX. 203.562.9377 • WWW.GENAISSANCE.COM

TO: Food and Drug Administration, Division of Dockets Management (HFA-305)

RE: Docket No. 2003D-0497

DATE: January 22, 2004

We are providing to FDA the following comments on the **Draft Guidance for Industry on Pharmacogenomic Data Submissions.**

1. Definitions of Known and Probable Valid Biomarkers

Definitions of "known valid biomarker" and "probable valid biomarker" are given in the glossary, and much of the guidance is couched in these terms. However, in some pharmacogenomic research, genetic markers are *not* thought of as biomarkers, at least not according to FDA definitions, i.e., as candidate surrogate endpoints (http://www.fda.gov/cder/Offices/Biostatistics/Chakravarty_376/). An example is the use of a DNA marker to stratify subjects into those suitable for treatment and those not. In this example, the marker is used as a diagnostic test and we would expect it to be held to the same standards to which other diagnostic tests are held. Hence, the definition of a biomarker in this document should be clarified, or different terminology developed. In addition, the document's definition of "known valid biomarker" requires "widespread agreement in the medical or scientific community." A validated diagnostic DNA marker developed by a sponsor would not need such widespread agreement, but merely support by regulatory bodies. A more concrete definition of "valid" would be instructive, and should include clarification of the most important piece: independent replication of results.

These definitions impact combination products in a similar fashion. For a drug/device combination product where the device is a pharmacogenetic test, it will be typical for the data supporting that test to be internally derived and known only by the product sponsor. In these cases, to what level of scientific validity will that data need to rise in order to be included on the drug label? To require that it be a "known valid biomarker," as defined in the guidance, would discourage the development of such products as sponsors will be forced to submit data for peer review and publication. On the other hand, the requirements for a marker to reach "probable valid biomarker" status are not well-defined. In addition, FDA should be clear that such devices will require approval by CDRH if the indication or the dosing depends on the results of the diagnostic.

2. Voluntary Genomic Data Submissions

While the guidance addresses criteria for sponsors of INDs, NDAs, and BLAs for voluntary genomic data submissions (VGDSs), it is less clear on whether the opportunity or the process exist for non-holders of regulatory dossiers to provide information to FDA in the form of a VGDS. Selected lines from the draft guidance are referenced here:

> Section III.A., line 147: "Many pharmacogenomics testing programs currently carried out by pharmaceutical sponsors or by scientific organizations (emphasis added) are intended to develop the knowledge base necessary to establish the validity of new genomic biomarkers.... scientific development of this sort is highly desirable for advancing understanding of relationships between genotype or gene expression and responses to drugs and, therefore, should be encouraged and facilitated. For these reasons...FDA is encouraging *voluntary submission* of such data...."
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> Section III.C., line 236: "Therefore, the FDA is requesting that sponsors (emphasis added) conducting such programs consider providing pharmacogenomics data to the Agency voluntarily...VGDSs can be used for the submission of pharmacogenomics studies that are not required to be submitted."
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> Section V, line 411: "The FDA invites submission of exploratory pharmacogenomic data on drugs or candidate drugs whether or not the drugs are currently the subject of an active IND, NDA, or BLA." (emphasis added)
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> Line 419, "The purpose of the VGDS is to provide the FDA access to emerging pharmacogenomics data (emphasis added) so that a foundation can be built for developing scientifically sound regulatory policies. The Agency intends to gain experience and to develop an aggregate genomic knowledge database from multiple VGDSs that could be used to rationally facilitate the use of pharmacogenomics in drug development and to share what general knowledge is learned from the data repositories, where appropriate."

If the goal of voluntary submissions is to facilitate FDA learning and experience with pharmacogenomics data, then a process must be defined to enable and encourage submission by non-sponsors, given the extensive capacity for research conducted by non-sponsors of regulatory dossiers. In fact, there appears to be little motivation under present circumstances for sponsors of INDs/NDAs/BLAs to submit a VGDS until the responsibilities and authority of the FDA Interdisciplinary Pharmacogenomic Review Group (IPRG) are clarified (see below); FDA might anticipate a paucity of VGDS submissions by sponsors and a majority by other organizations. We suggest that FDA create an atmosphere and a mechanism that allows and encourages VGDS submission by all interested parties and that the same or similar level of confidentiality be afforded all such submissions.

3. Authority and Responsibilities of FDA Interdisciplinary Pharmacogenomic Review Group

The statement that seems to cause the greatest degree of consternation within industry is line 503: "However, after the sponsor submits a VGDS, if additional information becomes available that renders the results required to be submitted...the sponsor must submit the data to the IND, NDA, or BLA...." The guidance also explains that the function of the IPRG (line 241) is "...to review VGDS, to work on ongoing policy development, and to advise review divisions dealing with pharmacogenomics data."

This plan raises questions for FDA:

- Will representatives of the Office of New Drugs or other sections of FDA have access to data submitted to the IPRG? If so, under what circumstances and how will they use the information?
- Will the IPRG pool data from multiple submissions or from outside sources that singly may not reach scientific validity? If those pooled results now are scientifically valid, how will this information be relayed to stakeholders, including both sponsors and other organizations that either conducted the studies or hold a vested interest in the outcomes? Under these circumstances, how will confidentiality be maintained? What right would a sponsor have to appeal regulatory decisions that result from this process?
- Do the reporting requirements differ for safety and efficacy results? In other words, will the measure of scientific validity (and therefore one's decision to submit a VGDS) differ depending on the risk/benefit ratio to public health?

4. Global Policies on Pharmacogenetics

While this guidance will define the policies FDA will apply for evaluation of pharmacogenomic and pharmacogenetic data, global policies are needed to prevent duplication of effort and multiplicity of formats and processes. Clearly a global regulatory position from ICH is indicated and we encourage FDA to pursue such a policy in accordance with the ICH process.

Respectfully submitted,

Carol R. Reed, MD, FACP, FCCP
Vice President, Medical Affairs

Bradley J. Dain, Ph.D.
Director of Clinical Biostatistics and Clinical Data Management